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Proline Catalyzed α-Aminoxylation Reaction in the Synthesis of Biologically Active Compounds

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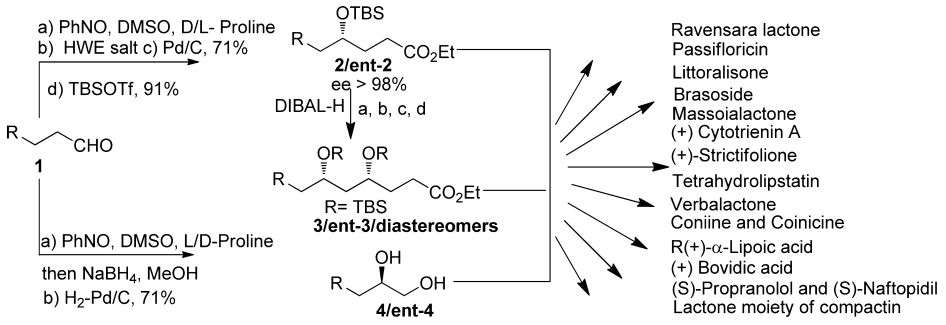
CONSPECTUS



The search for new and efficient ways to synthesize optically pure compounds is an active area of research in organic synthesis. Asymmetric catalysis provides a practical, cost-effective, and efficient method to create a variety of complex natural products containing multiple stereocenters. In recent years, chemists have become more interested in using small organic molecules to catalyze organic reactions. As a result, organocatalysis has emerged both as a promising strategy and as an alternative to catalysis with expensive proteins or toxic metals.

One of the most successful and widely studied secondary amine-based organocatalysts is proline. This small molecule can catalyze numerous reactions such as the aldol, Mannich, Michael addition, Robinson annulation, Diels–Alder, α-functionalization, α-amination, and α-aminoxylation reactions. Catalytic and enantioselective α-oxygenation of carbonyl compounds is an important reaction to access a variety of useful building blocks for bioactive molecules. Proline catalyzed α-aminoxylation using nitrosobenzene as oxygen source, followed by in situ reduction, gives enantiomerically pure 1,2-diol. This molecule can then undergo a variety of organic reactions. In addition, proline organocatalysis provides access to an assortment of biologically active natural products including mevinoline (a cholesterol lowering drug), tetrahydrolipstatin (an antiobesity drug), *R*(+)-α-lipoic acid, and bovidic acid.

In this Account, we present an iterative organocatalytic approach to synthesize both *syn*- and *anti*-1,3-polyols, both enantio- and stereoselectively. This method is primarily based on proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehyde to give a γ-hydroxy ester. In addition, we briefly illustrate the broad application of our recently developed strategy for 1,3-polyols, which serve as valuable, enantiopure building blocks for polyketides and other structurally diverse and complex natural products. Other research groups have also applied similar strategies to prepare such bioactive molecules as littoralisone, brasoside and (+)-cytotrienin A. Among the various synthetic approaches reported for 1,3-polyols, our organocatalytic iterative approach appears to be very promising and robust. This method combines the merit of organocatalytic reaction with an easy access to both enantiomerically pure forms of proline, mild reaction conditions, and tolerance to both air and moisture. In this Account, we present the latest applications of organocatalysis and how organic chemists can use this new tool for the total synthesis of complex natural products.

Introduction

Organocatalysis is rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulation. It is often associated with mild and simple reaction conditions that are appealing because of easy handling, cost and safety issues. Proline in

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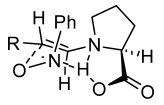
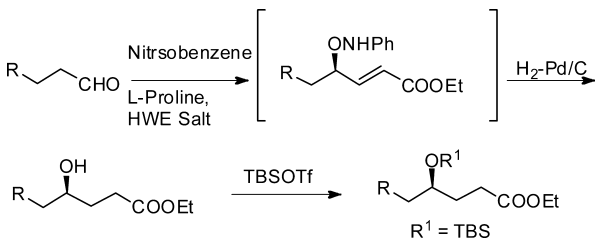


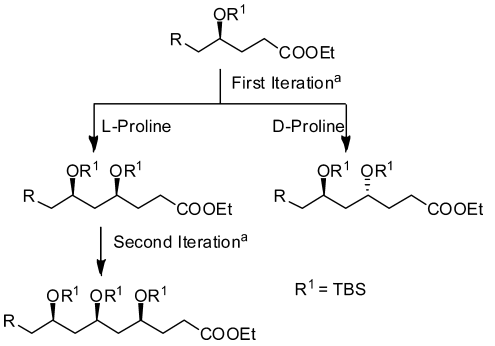
FIGURE 1. Proposed transition state of the reaction.

SCHEME 1. Synthesis of γ-Hydroxy Ester



the recent past has been defined as a "universal catalyst" because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products.[1] The 1,3-skipped polyol systems containing *anti* or *syn* configurations are structural motifs of several natural products including valuable polyene macrolide antibiotics. The metal mediated direct introduction of oxygen atom adjacent to the carbonyl group in a catalytic and enantioselective manner using both chiral Lewis acid and Lewis base represents a valuable advance in synthetic methodology.[2] Zhong for the first time applied proline to α-aminoxylation reaction; he also established a methodology to prepare *O*-amino substituted allylic alcohol by α-aminoxylation of carbonyl compound followed by Horner–Wadsworth–Emmons (HWE) olefination.[3] We have further extended the scope of this reaction and recently developed a practical and efficient iterative approach to prepare enantiomerically pure both *syn*/*anti*-1,3-polyols via proline-catalyzed sequential α-aminoxylation of carbonyl compound followed by HWE olefination. In this protocol, an aldehyde is subjected to α-aminoxylation by sequential treatment with nitrosobenzene using L- or D-proline as catalyst followed by HWE olefination reaction to give *O*-amino substituted allylic alcohol, which is subjected to hydrogenation conditions using catalytic amount of Pd/C to furnish the γ-hydroxy ester in high enantioselectivity and excellent yield (Scheme 1). The observed enantioselectivity of the catalytic α-aminoxylation can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *si* face of an enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxylation with R configuration (Figure 1).[3b] It may be pertinent to mention here that organocatalytic tandem α-aminoxylation reaction with

SCHEME 2. Iterative Strategy for the Synthesis of 1,3-Polyols[a]



[a]One cycle of iteration is composed of a four-step sequence: (1) DIBALH, reduction of ester; (2) nitrosobenzene, D/L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (3) H_2/Pd–C, EtOAc; (4) TBSOTf, 2,6-lutidine, DCM.

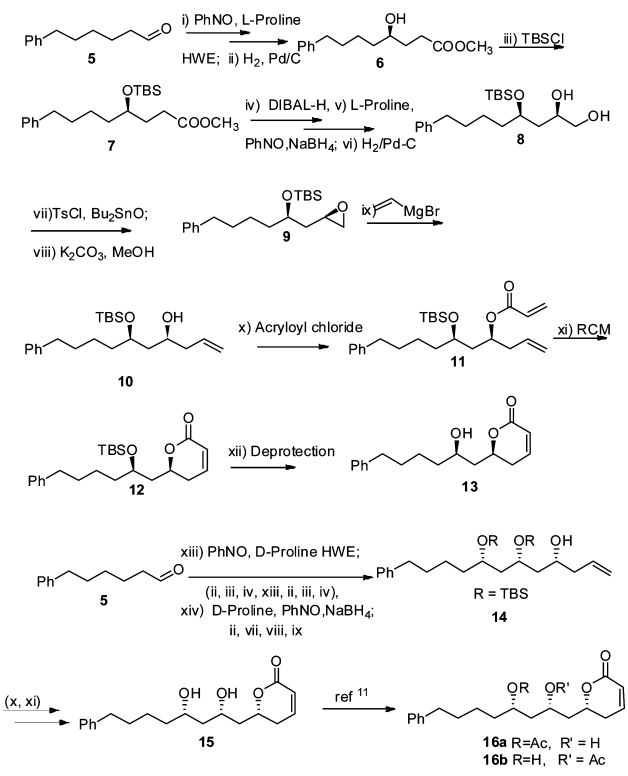
nitrosobenzene in desymmetrization of prochiral ketones is known to bring the concomitant heterolytic O–N bond cleavage furnishing the α-hydroxy ketone in a single step.[4] Thus this process is particularly attractive because of its predictable stereochemistry and avoidance of discrete deprotection step.

After free hydroxy group protection of γ-hydroxy ester as TBS ether, it is subjected to first cycle of iteration (consisting of four step sequences) using L- or D-proline to furnish *syn*/*anti*-1,3-diol (Scheme 2).[5]

The scope of this reaction was examined with different substrates, and it was observed that the reaction sequence displayed a wide substrate scope with excellent diastereomeric ratio and good yields. While *anti*/*syn*-1,3-diols were obtained in >39:1 ratio using D-proline as catalyst, less selectivity (*syn*/*anti*:10:1) was observed with the use of L-proline as catalyst. Presumably, the considerable steric bulk on incoming oxygen source coupled with the steric bulk of the silyl protecting group on the hydroxyl group might be possible cause of lowering the selectivities in the case of syn isomer. Since the stereochemical outcome of the reaction can be predicted on the basis of the catalyst used, this method gives an easy access to *syn*/*anti*-1,3-diols with predictable and useful stereocontrol in good yield. Thus using this protocol, in principle, all possible combinations of 1,3,5-polyols can be accessed (Scheme 2).

This method has several advantages over the most widely used method to prepare 1,3-polyols in an iterative fashion like allyl addition sequence utilizing stoichiometric amounts of chiral borons[6a] and titanium,[6b] catalytic iterative synthetic routes using Overman esterification,[6c] and chromium mediated asymmetric allylation,[6d] including our own method by iterative hydrolytic kinetic resolution of racemic

SCHEME 3. Synthesis of (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and *Ravensara* Lactones

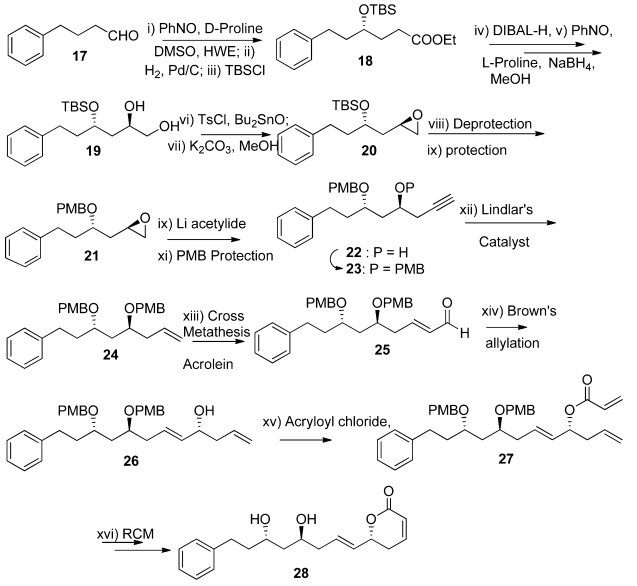


epoxide.[6e] We have applied proline catalyzed α-aminoxylation of aldehyde and also the protocol developed by us for *syn*/*anti*-1,3-polyols to synthesize a variety of biologcally active natural products which follow.

Applications

Synthesis of (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and Ravensara Lactones. (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one **13** was isolated from *Ravensara crassifolia*.[7] Our strategy to assemble this molecule is based on proline catalyzed α-aminoxylation reaction to generate the required stereocenters and ring-closing metathesis of acrylate esters using Grubb's catalyst. In our synthesis. phenyl hexanal **5** was subjected to sequential α-aminoxylation (L-proline as a catalyst) followed by HWE olefination reaction and hydrogenation using a catalytic amount of Pd/C to furnish the γ-hydroxy ester **6**. TBS protection of the hydroxy group eventually furnished the silyl protected γ-hydroxy ester **7**. Ester **7** was reduced with DIBAL-H to furnish the corresponding aldehyde which was subjected to α-aminoxylation catalyzed by L-proline followed by in situ reduction using $NaBH_4$ and Pd/C reduction to afford diol **8.** Diol **8** on selective monotosylation and base treatment furnished epoxide **9**

SCHEME 4. Total Synthesis of (+)-Strictifolione



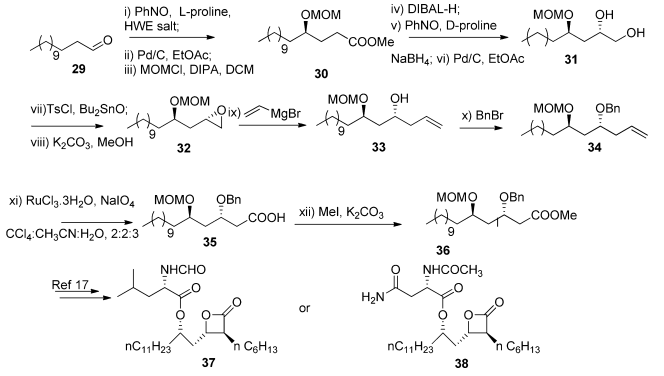
in 82% yield. Regioselective ring-opening of epoxide **9** with vinylmagnesium bromide gave homoallylic alcohol **10** which was esterified as acryloyl ester **11**. Subsequent ring-closing metathesis with Grubb's catalyst afforded the α,β-unsaturated δ-lactone **12** in 92% yield. Finally desilylation was achieved by treatment of **12** with *p*-TSA to yield the target molecule **13**[8] (Scheme 3).

Ravensara lactones **16a** and **16b**[9] have been isolated from *Ravensara anisata*. Their biological activities include plant growth inhibition, antifeedant, antifungal,[10a] cytotoxicity against human tumor cells,[10b] and inducing apoptosis.[10c] Employing a similar iterative strategy as described above, we have accomplished the total synthesis of ravensara lactones **16a** and **16b**. Thus, starting from phenyl hexanal **5** and using D-proline as a catalyst, all three stereogenic centers were generated in an iterative fashion following a similar sequence of reaction as described above to give **14** which was eventually converted into **15** via ring closing metathesis. Since the monoacetylation of lactone **15** to the target molecules has already been reported,[11] this constitutes the formal synthesis of **16a** and **16b**[8] (Scheme 3).

Total Synthesis of (+)-Strictifolione. Aimi et al. isolated (+)-strictifolione from the stem bark of *Cryptocaria strictifolia* in Indonesia.[12] The molecule has been shown to display antifungal activity. The total synthesis of strictifolione commenced with aldehyde **17** which was subjected to α- aminoxylation (D-proline), HWE olefination, and Pd/C reduction to furnish γ-hydroxy ester in good yield and >98% ee. The free hydroxyl group was then protected as silyl ether **18** (Scheme 4).

Ester **18** on reduction with DIBAL-H furnished aldehyde which on further α-aminoxylation was catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ resulting in *O*-amino-substituted diol in 71% yield and >95% de. Finally, reductive hydrogenation afforded the diol **19**. Epoxidation of compound **19** followed by TBS deprotection and PMB protection furnished compound **21**. The opening of epoxide **21** with lithium acetylide followed PMB protection and partial reduction of triple bond with Lindlar's catalyst led to compound **24**. Cross metathesis of olefin **24** with acrolein afforded the α,β-unsaturated aldehyde **25** in 76% yield with an *E*/*Z* ratio of >30:1. Brown's allylation on aldehyde **25** generated homoallylic alcohol **26** in 74% yield with diastereomeric ratio 96:4. Further esterification with acryloyl chloride followed by RCM and PMB deprotection afforded strictifolione **28**. The relative stereochemistry of the 1,3-diol function at C4′ and C6′ was elucidated from the ^{13}C NMR spectrum of the acetonide derivative, while the configurations of their stereogenic centers were deduced by the Mosher method.[13]

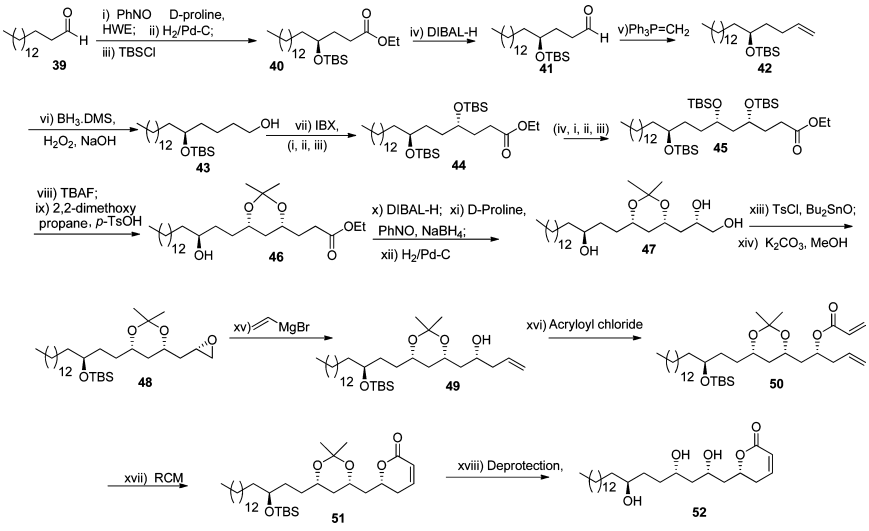
SCHEME 5. Synthesis of Tetrahydrolipstatin and Tetrahydroesterastin



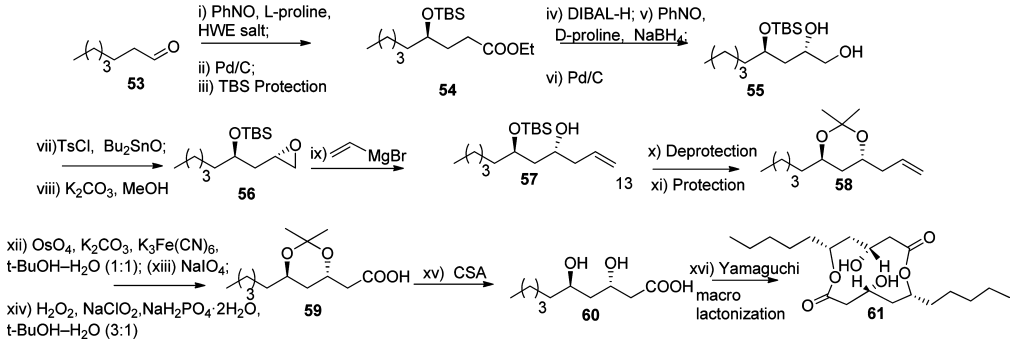
Synthesis of Tetrahydrolipstatin and Tetrahydroesterastin. Lipstatin and esterastin, antiobesity drugs, are β-lactone analogous 3,4-disubstituted 2-oxetanones isolated from *Streptomyces* species[14] differing only in the structure of C-4 side chain and the nature of the amino acid linked to it. The saturated derivatives[15] of tetrahydrolipstatin and tetrahydroesterastin exhibit comparable pharmacological properties. We have developed an innovative route for the synthesis of the target molecule[16] starting from aldehyde **29** which was subjected to α-aminoxylation using L-proline as catalyst followed by HWE olefination and Pd/C reduction to generate γ-hydroxy ester. The γ- hydroxy ester was protected as MOM ether to give **30** in 89% yield (Scheme 5). Compound **30** on reduction with DIBAL-H furnished aldehyde which on α-aminoxylation catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ and reductive hydrogenation with Pd/C afforded the diol **31** in 85% yield. The diol **31** was epoxidized and subjected to vinyl Grignard reaction to furnish homoallylic alcohol **33**. Benzyl protection of **33** followed by oxidative cleavage of double bond led to acid **35** in 85% yield. Esterification of acid with methyl iodide yielded compound **36**. The conversion of **36** to **37** and **38** is already reported in literature.[17]

Synthesis of Passifloricin A. Passifloricin A, was isolated by Echeverri et al.[18] from the resin of *Passiflora fetida*, from the family *Passifloraceae*. We have accomplished the synthesis of passifloricin A starting from aldehyde **39** which on α-aminoxylation and various functional group transformations afforded ester **40** (Scheme 6). The compound **40** on

SCHEME 6. Synthesis of Passifloricin



SCHEME 7. Synthesis of Verbalactone

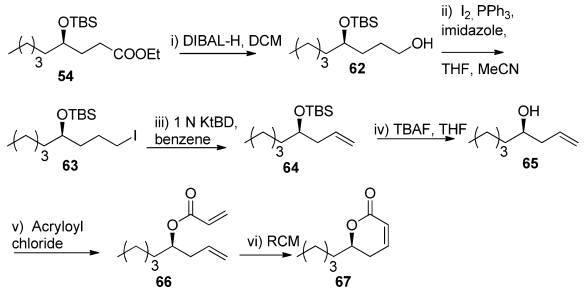


reduction, Wittig reaction, and hydroboration oxidation reaction generated **43**. Oxidation of alcohol **43** to aldehyde followed by two consecutive iterative α-aminoxylation, HWE olefination, and reduction cycles afforded **45** in 65% yield and in 92% de. Desilylation of **45** and subsequent DMP protection yielded **46** in 85% yield. The DIBAL-H reduction of compound **46** followed by proline catalyzed diol formation furnished compound **47** in 85% yield. Routine functional group transformations like tosylation followed by epoxidation and vinyl Grignard reaction generated homoallylic alcohol **49**. Conversion of hydroxy group into acrylate and subsequent RCM followed by deprotection afforded the target molecule **52** in overall 4.7% yield.[19]

Synthesis of Verbalactone. Verbalactone was isolated by Mitaku and co-workers from the roots of *Verbascum undulatum*.[20] It displays antibacterial activity against three Gram positive bacteria with optimum activity MIC 62.6 μg/mL and five Gram negative bacteria with optimum activity MIC 125 μg/mL. The synthesis of molecule started from *n*-heptanal **53** via L-proline-catalyzed α-aminoxylation, HWE olefination, and reduction followed by protection of free hydroxy groups to give ester **54** in 68% yield and 97% ee (Scheme 7). The resulting ester **54** underwent proline catalyzed diol formation **55** in 78% yield with >95% de. Diol **55** on monotosylation followed by base treatment afforded epoxide **56** in 82% yield. The reaction of epoxide with vinyl magnesium bromide followed by deprotection of TBS group and acetonide protection gave the desired compound **59** in 92% yield. Oxidation of olefinic double bond furnished the corresponding acid which was converted to verbalactone **61** after deprotection and Yamaguchi macrolactonization.[21]

Synthesis of Massoialactone. Massoialactone was isolated for the first time by Abe from the bark of *Cryptocarya massoia*.[22] It is a skin irritant and produces systolic standstill in frog heart muscle. Recently, we developed a practical and enantioselective synthesis of massoialactone from the

SCHEME 8. Synthesis of Massoialactone

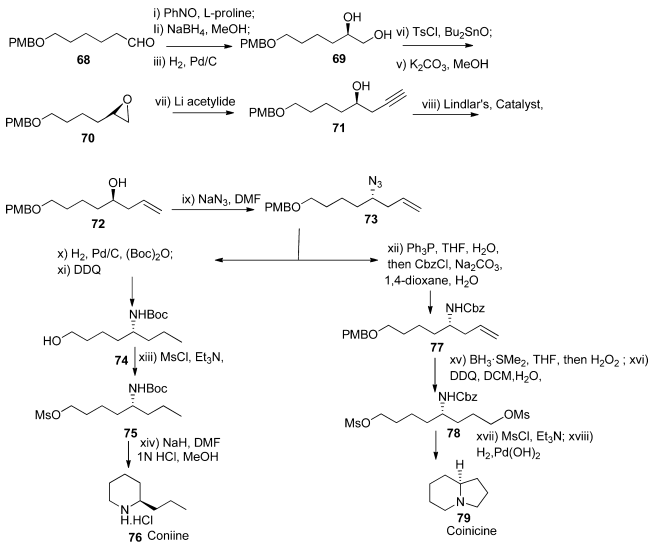


common precursor **54** which on DIBAL-H reduction and iodination reaction generated **63** (Scheme 8). Iodo compound **63** on elimination and TBS deprotection generated homoallylic alcohol **65** which on esterification and RCM reaction gave massoialactone **67**.[21]

Synthesis of (*R*)-Coniine and (*S*)-Coinicine. (*R*)-Coniine and (*S*)-coinicine are the simplest members of the piperidine and indolizidine alkaloids, respectively.[23] The synthesis began with the aldehyde **68** which on α-aminoxylation and in situ reduction with sodium borohydride and Pd/C reduction resulted in diol **69** (Scheme 9). Known transformations like epoxidation followed by opening with lithium acetylide and partial reduction of triple bond afforded **72**.

The alcohol **72** was converted to azido compound **73** with inversion of stereochemistry, which is a common precursor for both the target molecules. For the synthesis of (*R*)-coniine, double bond was reduced followed by in situ conversion of azide to amine. The free amine was protected as *t*-butyl carbamate which on subsequent PMB deprotection furnished alcohol **74** in 80% yield. Compound **74** on mesylation and base treatment gave boc protected coniine. Finally boc deprotection generated (*R*)-coniine **76**.[24] Similarly, for the synthesis of (*S*)-coinicine **79**, the azide **73** under Staudinger reaction conditions was converted to free amine which was further protected as its benzyl carbamate.

SCHEME 9. Synthesis of (R)-Coniine and (S)-Coinicine



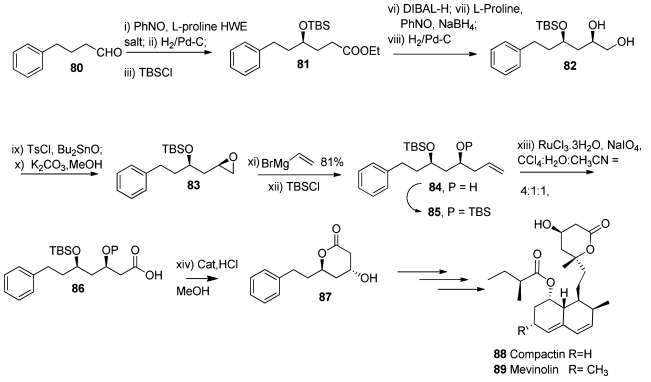
Olefin **77** was subjected to hydroboration oxidation reaction which on PMB deprotection gave diol in 74% yield. Diol on mesylation furnished dimesyl compound 7**8** in 84% yield. Finally, benzyl carbamate deprotection and concomitant cyclization under hydrogenation conditions afforded (*S*)-coinicine **79**.[24]

Synthesis of Lactone Moiety of Compactin and Mevinolin. Compactin and mevinolin have unique ability to lower blood cholesterol levels, especially plasma low-density lipoprotein (LDL)[25] cholesterol in human beings and is important for the mitigation of arteriosclerosis.

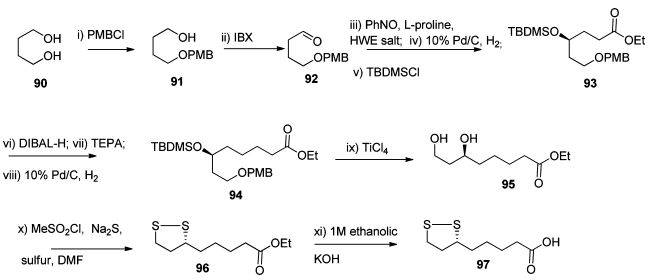
The key structural feature of such a bioactive molecule is chiral β-hydroxy-δ-lactone moiety **87**. We have reported an organocatalytic route for the synthesis of lactone moiety of compactin and mavinolin starting from aldehyde **80** which on α- aminoxylation, HWE olefination, Pd/C reduction, and TBS protection afforded compound **81** (Scheme 10). Ester **81** was reduced and subjected to α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the *O*-amino-substituted diol in overall 70% yield and 92% de, which under reductive hydrogenation conditions afforded diol **82** in 92% yield. Diol **82** was smoothly converted to the desired epoxide via monotosylation and base treatment. The opening of epoxide with vinyl Grignard reaction followed by silyl protection furnished compound **85**. The oxidation of double bond to acid and finally lactonization of acid afforded chiral β-hydroxy-δ-lactone moiety **87**.[26] The transformation of **87** to **88** and **89** is already documented in literature.[27]

Synthesis of (*R*)-(+)-α-Lipoic Acid. α-Lipoic acid was isolated by Reed and co-workers from liver residue.[28] Lipoic

SCHEME 10. Synthesis of Lactone Moiety of Compactin and Mevinolin



SCHEME 11. Synthesis of (*R*)-(+)-α-Lipoic Acid

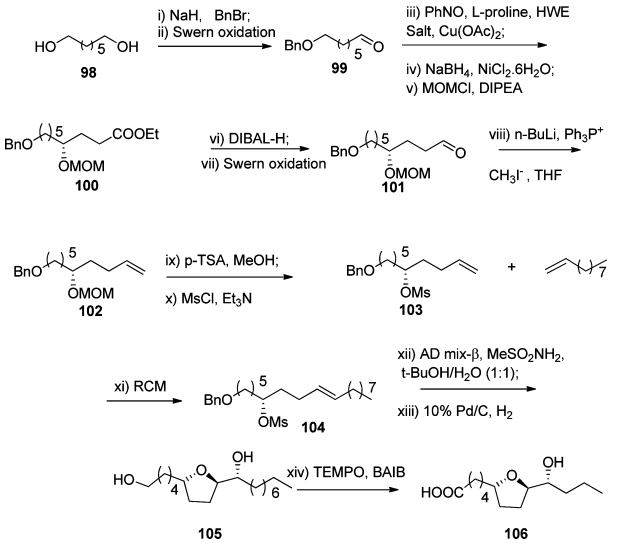


acid and its derivatives are highly active as anti-HIV and antitumor agents. The *R*-(+)-enantiomer is more effective than the *S*-(−)-enantiomer for enhanced insulin-stimulated glucose transport and nonoxidative and oxidative glucose metabolism.[29]

Chavan and co-workers employed proline catalyzed α-aminoxylation reaction for the synthesis of (*R*)-(+)-α-lipoic acid. The starting material 1,4-butanediol **90** was subjected to monoprotection followed by oxidation of alcohol to aldehyde **92** (Scheme 11). The aldehyde on α-aminoxylation with L-proline, HWE olefination, and reduction resulted in γ-hydroxy ester in 58% yield and 97% chiral purity. The free hydroxyl group was protected as TBDMS to afford **93** in 89% yield. The ester **93** on two carbon homologation furnished compound **94**. Global deprotection followed by dimesylation and further treatment with sodium sulfide and elemental sulfur in DMF afforded (*R*)-(+)-α-lipoic acid **97** in overall 16.6% yield.[30]

Total Synthesis of (+)-18-(6*S*,9*R*,10*R*)-Bovidic Acid. Natural insect repellent (+)-bovidic acid was isolated by Oliver and Nakanishi from the pelage and skin of a gaur *B. Frontalis*.[31] Yadav et al. have reported the synthesis of bovidic acid starting from 1,7-hepatanediol **98** (Scheme 12). Monoprotection of primary hydroxy group, Swern oxidation

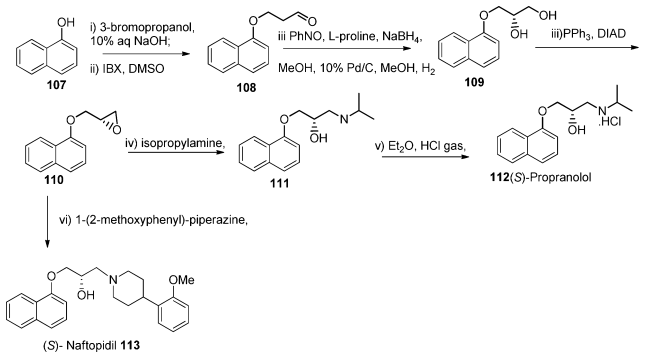
SCHEME 12. Synthesis of (+)-18-(6*S*,9*R*,10*R*)-Bovidic Acid



followed by α-aminoxylation, HWE olefination resulted in γ-hydroxy-α,β-unsaturated ester (96% ee, HPLC) in 48% yield. The selective reduction of the double bond in γ-hydroxy-α,β-unsaturated ester using $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ afforded γ-hydroxyl ester in 90% yield which was further protected as MOM ether to give **100**. Subsequent ester reduction, Swern oxidation, and Wittig reaction furnished **102**. Known functional group manipulations like deprotection of MOM ether followed by mesylation gave compound **103**. Metathesis of 1-decene and olefinic compound **103** generated **104** in 75% yield (*E*/*Z* isomers = 15:1). Sharpless asymmetric dihydroxylation on **104** followed by debenzylation and TEMPO-BAIB oxidation afforded (+)-bovidic acid **106**.[32]

Synthesis of β-Blockers: (*S*)-Propranolol and (*S*)-Naftopidil. β-Adrenergic blocking agent (*S*)-propranolol and (*S*) naftopidil are part of a group of drugs whose biological activity is associated with only the (*S*)-enantiomer rather than the (*R*)-isomer.[33] Synthesis of 3-aryloxy-1,2-propanediol **109** was accomplished using proline-catalyzed α-aminoxylation on aldehyde **108** followed by in situ reduction using $NaBH_4$ to furnish the *O*-amino-substituted diol which on reductive hydrogenation afforded the diol **109** in 79% yield over two steps and >98% enantiomeric purity (Scheme 13). The aldehyde **108** in turn was obtained by reacting α-naphthol with 3-bromopropanol to give alcohol which on IBX oxidation furnished aldehyde **108.** Diol **109** was converted to epoxide **110** using Mitsunobu conditions followed by treatment with isopropylamine to give compound (*S*)-propranolol **111** in 83% yield and >98% ee which on treatment with anhydrous HCl gas afforded (*S*)-propranolol hydrochloride **112**.[33c] Finally (*S*)-naftopidil was obtained on reaction of epoxide **110** with

SCHEME 13. Synthesis of β-Blockers: (*S*)-Propranolol and (*S*)-Naftopidil

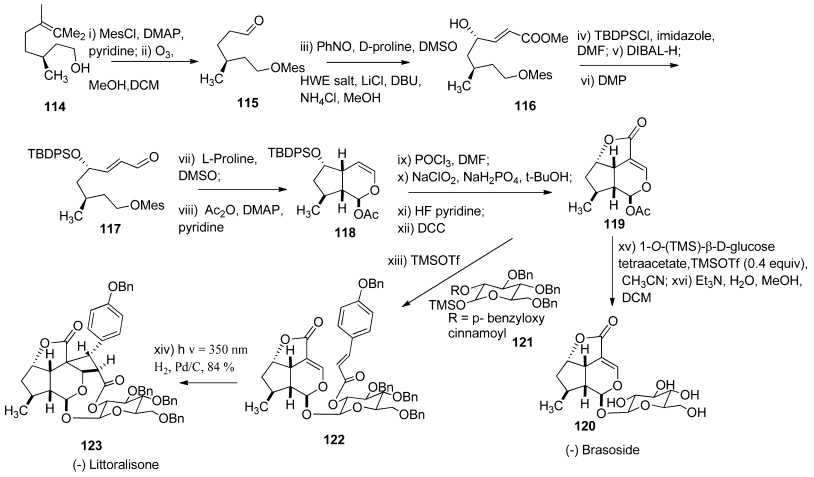


1-(2-methoxyphenyl)-piperazine to give the target molecule **113** in 85% yield and >98% ee.

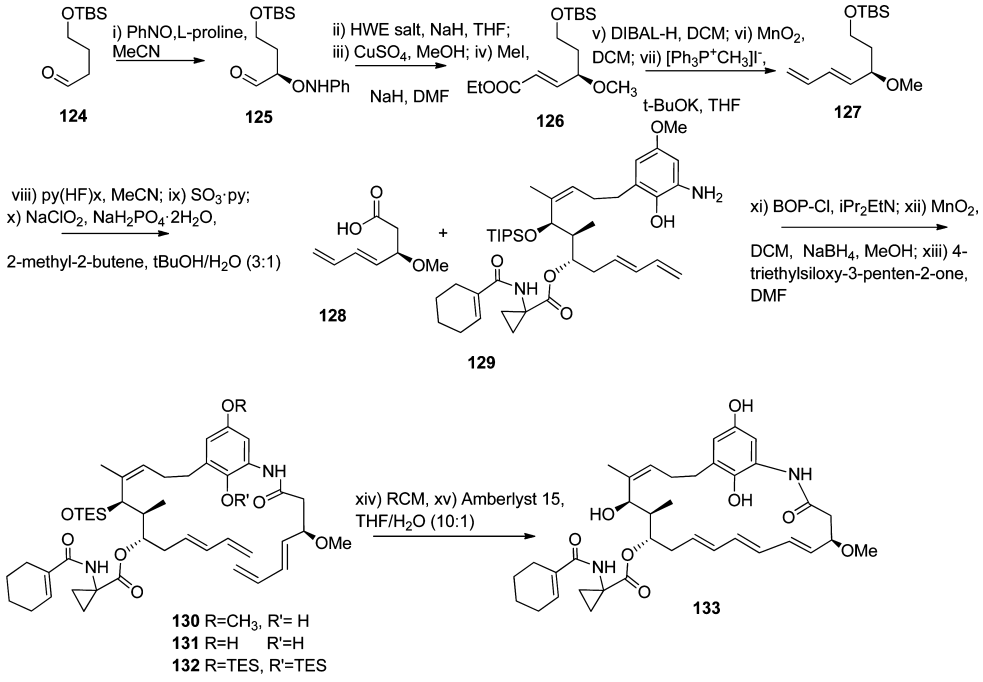
Synthesis of Littoralisone and Brasoside. Littoralisone, isolated in 2001, is the active agent for increased NGF-induced neurite outgrowth in PC12D cells.[34] Littoralisone is presumed to be biochemically derived from brasoside,[35] but no relevant intermediates to support this pathway have been found to date. MacMillan reported the synthesis of these molecules starting from (−)-citronellol. Thus, the protection of (−)-citronellol **114** as its mesitoate ester followed by ozonolysis furnished aldehyde **115** which was subjected to α-aminoxylation reaction, HWE olefination, and subsequent reduction to generate compound **116** (Scheme 14). Protection of free hydroxy as TBDPS ether followed by DIBAL-H reduction and DMP oxidation afforded formyl-enal Michael substrate **117**. Compound **117** on reaction with L-proline in DMSO furnished lactol in 91% yield with 10:1 *cis*-selectivity which on in situ acetylation resulted in compound **118** in 83% yield. Conversion of iridoid **118** to lactone was carried out in four steps by known functional group transformations affording **119** in 56% yield. Iridoid **119** was coupled with 1-*O*-(TMS)-β-D-glucose tetracetate, which on further deacetylation furnished (−)-brasoside. The glycosidic union of **119** and **121**[36] was accomplished via TMSOTf to provide the desired glucose-tethered diene **122** in 74% yield. Finally, intramolecular [2 + 2] photocycloaddition on **122** followed by in situ hydrogenolysis furnished synthetic (−)-littoralisone **123** as a single isomer in 84% yield.[37]

Total Synthesis of (+)-Cytotrienin. Cytotrienin A **133** is a microbial antitumor secondary metabolite that was isolated from the fermentation broth of *Streptomyces* sp. RK95-74 from soil.[38] Hayashi et al. first reported the total synthesis of this molecule.[39] Proline-mediated α-aminoxylation of aldehyde **124** proceeded efficiently to provide **125** (Scheme 15). Under Horner−Emmons reaction conditions, a crude sample of **125** was converted into alcohol in 46% yield (over 3 steps)

SCHEME 14. Synthesis of Littoralisone and Brasoside



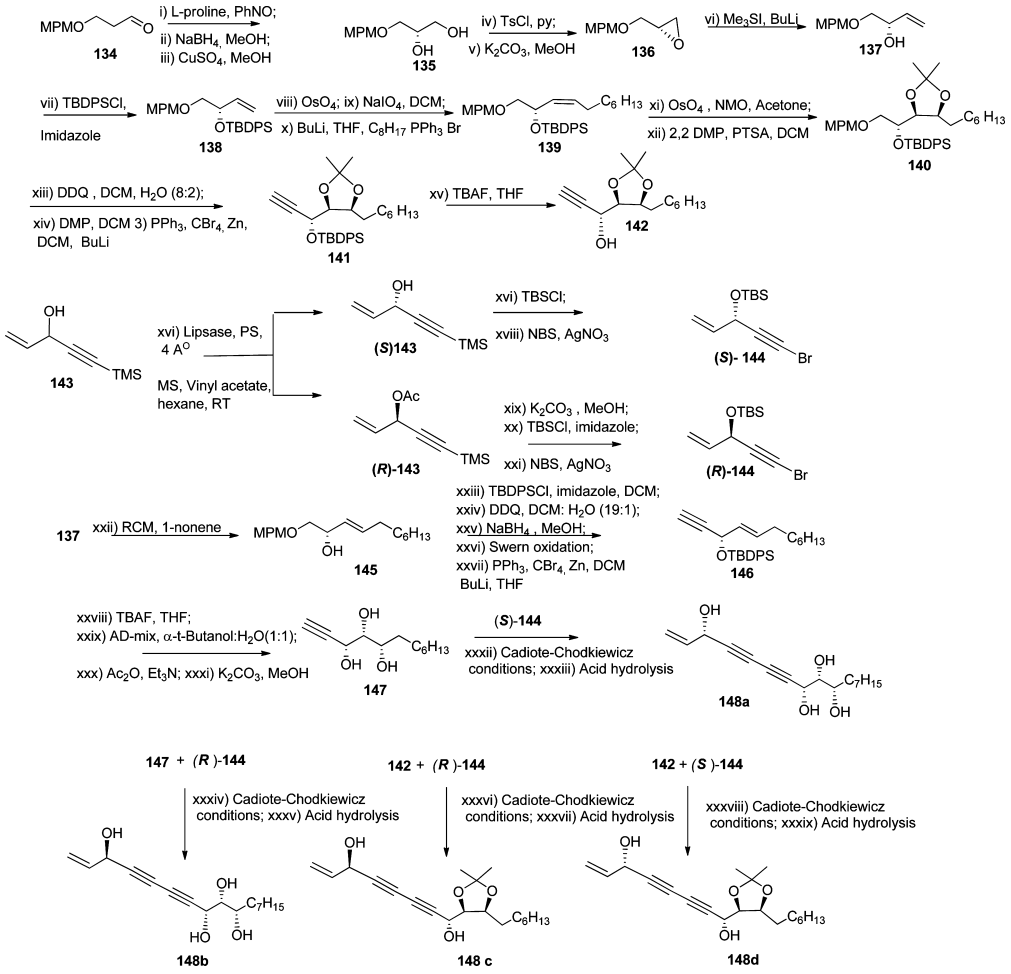
SCHEME 15. Synthesis of (+)-Cytotrienin A



with 98% ee which on Williamson ether synthesis afforded **126**. Reduction of **126** with DIBAL-H, oxidation with MnO_2, and Wittig reaction furnished diene **127**. Removal of TBS group, oxidation with SO_3pyridine, and subsequent Pinnick oxidation furnished the required acid **128**. The amine **129** (whose synthesis is already reported by Hayashi et al.[39]) was treated with carboxylic acid **128** in the presence of BOP-Cl to afford **130** in 79% yield (over 2 steps). The protecting group of phenol was converted from methyl to labile TES group by oxidation and subsequent reduction to hydroquinone **131**, followed by immediate protection of **131** with 4-triethylsiloxy-3-penten-2-one.[40] RCM reaction with Grubbs catalyst afforded triene in 39% yield which on removal of the TES group furnished (+)-cytotrienin A **133** in 95% yield.[39]

Synthesis of Heptadeca-1-ene-4,6-diyne-3*S*,8*R*,9*S*,10*S*-tetrol and Its Congeners. This class of natural products exhibit diverse biological profiles including potent cytotoxicity. The enantioenriched secondary alcohol **137**[41] was synthesized via routine α-aminoxylation reaction on propanal **134** followed by reduction to afford **135** (Scheme 16). The compound **135** on tosylation followed by reaction with K_2CO_3 in methanol and Corey Chaykovsky reaction furnished **137**

SCHEME 16. Synthesis of Heptadeca-1-ene-4,6-diyne-3*S*,8*R*,9*S*,10*S*-tetrol and Its Congeners



which was protected as silyl ether to generate **138**. Oxidative cleavage followed by reaction with triphenylphosphonium salt[42] and *p*-methoxybenzyloxy propanal gave (*Z*)-olefin **139** (*Z*/*E* 92:8). cis-Hydroxylation was achieved under the Upjohn conditions[43] followed by protection of diol as acetonide to furnish **140**. Compound **140** on deprotection of MPM group followed by oxidation and subsequent conversion into acetylene using Corey Fuchs protocol provided the corresponding alkyne **141** in 78% yield which on desilylation afforded **142** in 94% yield. The compound **143** on enzymatic resolution[44] resulted in acylated compound (*R*)-**143** in 35% yield with 98% optical purity, leaving enriched (*S*)-**143** in 36% yield with 98% optical purity. After the protection of alcohol, TBS-ether followed by Isobe's[45] procedure led to the desired (*S*)-**144** in 92% yield. Cross-metathesis between (*S*)-**137** and 1-nonene generated *E*-allylic alcohol **145** (*E*/*Z* 95:5) in 81% yield. The secondary alcohol **145** was protected as TBDPS ether. Oxidative cleavage followed by oxidation of primary alcohol under the Swern conditions furnished aldehyde which was subsequently subjected to Corey Fuchs protocol to furnish the corresponding acetylene **146** in 74% yield. Fluoride ion induced deprotection followed by catalytic asymmetric dihydroxylation led to desired intermediate **147** in 36% yield.[46] The triol **147** was cross-coupled with (*S*)-**144** or (*R*)-**144** employing Cadiote Chodkiewicz conditions, and subsequent acid-catalyzed deprotection resulted in **148a** and **148b**. Similarly, applying Cadiote Chodkiewicz conditions, compound **142** was coupled with (*S*)-**144** or (*R*)-**144** and hydrolyzed to furnish the target molecule **148c** and **148d**, respectively.[47]

Conclusion

We have shown that the proline catalyzed α-aminoxylation method has broad application in organic synthesis. We developed a novel practical and highly enantio- and diastereoselective tandem synthetic strategy for both *syn*- and *anti*-1,3-polyols using iterative proline catalyzed α-aminoxylation reaction. The protocol leading to 1,2-diol/1,3-polyols was utilized for the synthesis of a variety of natural products

with broad range of biological activity. In view of easy availability of proline and the simplicity of the reaction, α-aminoxylation directed domino reaction will continue to play an important role in asymmetric synthesis. We anticipate many more applications of the method to emerge in the near future, and this Account just presents the state of the art knowledge on how a synthetic organic chemist can exploit this novel tool for the total synthesis of complex natural products.

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FOOTNOTES

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The authors declare no competing financial interest.

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